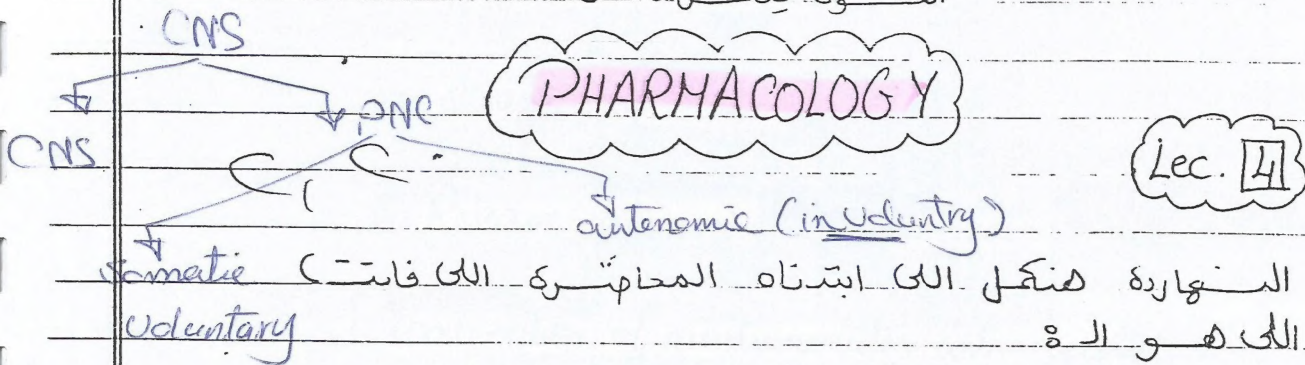


"الله الذي خلق اطراف الارض لا يكل ولا يعبأ ، يعطي المعنى قدرته ولحمه القوة يكسر شدة"



## Autonomic Nervous System

### Pharmacological Considerations

- \* By using drugs that mimic or block (lytics) the action of chemical transmitters, we can modify many autonomic functions.
- \* These functions involve variety of effector tissues including cardiac muscle, smooth muscle, exocrine glands, presynaptic nerve terminals.

نحن اننا ممكن استعمل ادوية بتشابه chemical transmitters لتتحكم في ال response التي بتطلع ، بس ده طبعا من ال smooth m. وال cardiac m. وال glands الهم انهم عن ال skeletal m.

- \* Autonomic drugs are useful in many clinical conditions. Conversely, a very large no. of drugs used for other purposes (not autonomic drugs) have unwanted effects on autonomic function.

نحن في ادوية هتعمل من autonomic زي مثلاً ، نحن ادوية ال heart ممكن يكونوا بيؤثر autonomic ، تأثير من دلو ، و يوقف اي مرحلة من مراحل طلوع ال neurotransmitter يعني ايه ؟!







## Drugs that interfere with specific steps in Chemical Transmission:

Transmission step	Sympathetic Adrenergic Nerves	Para-sym. Cholinergic Nerves
1. Synthesis of transmitter	$\alpha$ -methyl dopa	Reserpine <sup>Reserpine</sup> Hemicholinium <sup>hemicholinium</sup>
2. Storage of NT <sup>(*)</sup>	Reserpine (alkaloid) (antihypertensive drug)	None known
3. Release of trans.	Guanethidine	Botulinum toxin Botulinum toxin
4. Combination of trans. to receptor	$\alpha$ -propranolol ( $\alpha$ -receptors blocker) ( $\beta$ -propranolol ( $\beta$ -receptors blocker) (used as antihypertensive drugs)	Atropine (muscarinic) d-tubocurarine (nicotinic receptor) d-tubocurarine
5. Destruction or removal of trans from site of action	Tolcapone (COMT inhibitor) phenelzine (MAO inhibitor) Tricyclic antidepressants (inhibit neuronal transport)	physostigmine (cholinesterase inhibitor) physostigmine

COMT  $\rightarrow$  Catechol O-methyl transferase.

MAO  $\rightarrow$  Monoamine Oxidase.

- <sup>(\*)</sup> The transmitter after being synthesized must be stored in vesicles to be used to avoid being destroyed by the enzymes.  $\rightarrow$  then this NT is released due to  $Ca^{+2}$  ions

ooooo w k f j g h i j k l m n o p q r s t u v w x y z



## Adrenergic (symp.)

- $\alpha$  methyl dopa
- reserpine
- Guanethidine
- [ prazosin
- [ propranolol
- [ telcaptopone
- [ phelipine
- Tricyclic

## Cholinergic (para. -

- hemicholinium
- 
- Bethanidine toxin
- [ Atropine
- [ d tubocurarine
- physostigmine



Teserpine  
ethidine

hemichinam

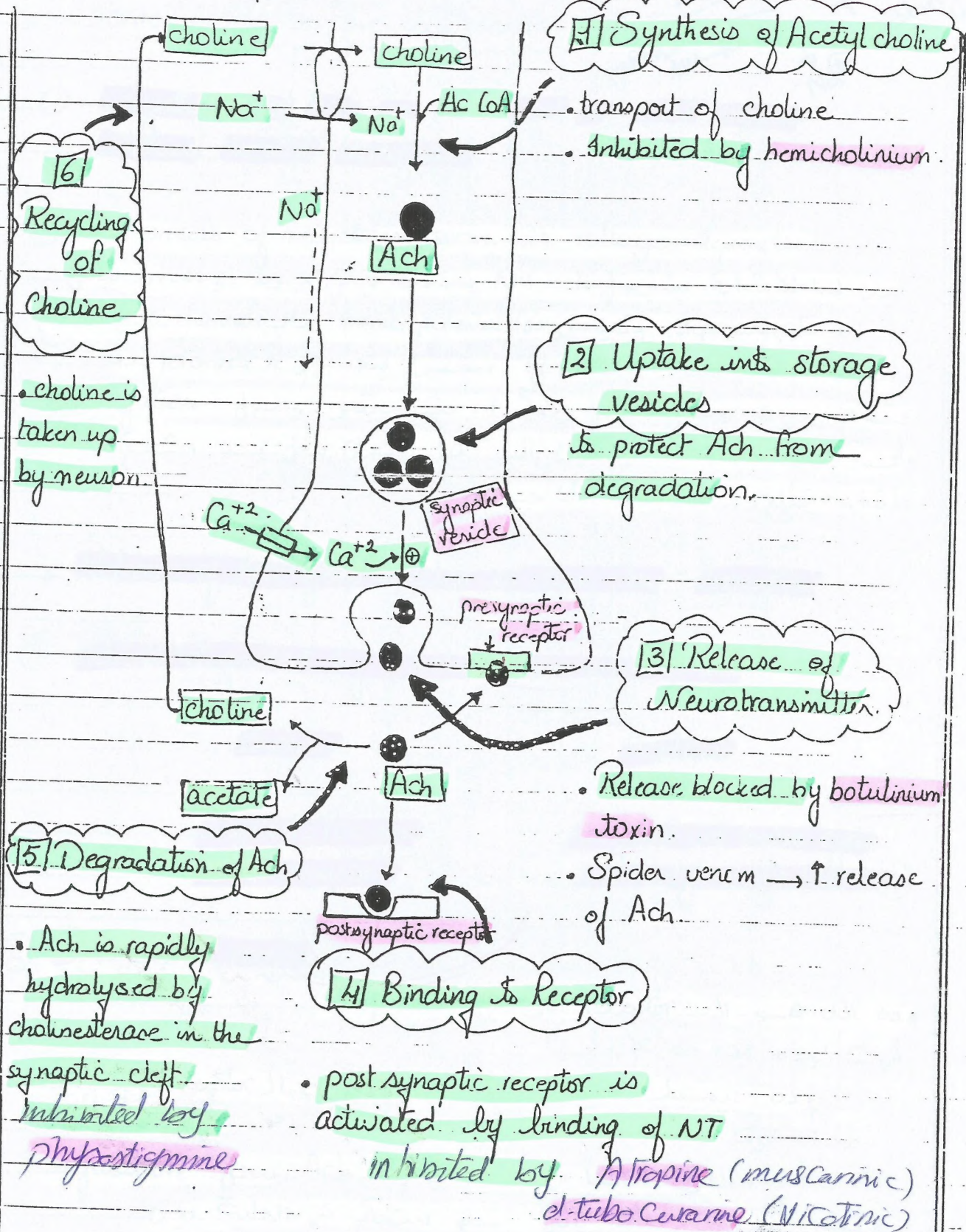
MAO  $\rightarrow$  Monoamine Oxidase

Toluene  
phenyl

مستوف رسمة توضیح ک ۵۵۵۵



# \*\* Cholinergic Transmission \*\*

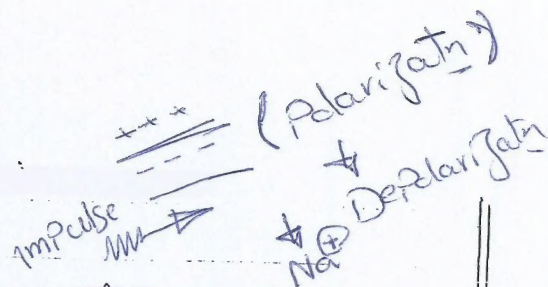




AT → Synthesis  
Cholinesterase → degradation

-5-

\* Some Notes on the diagram:

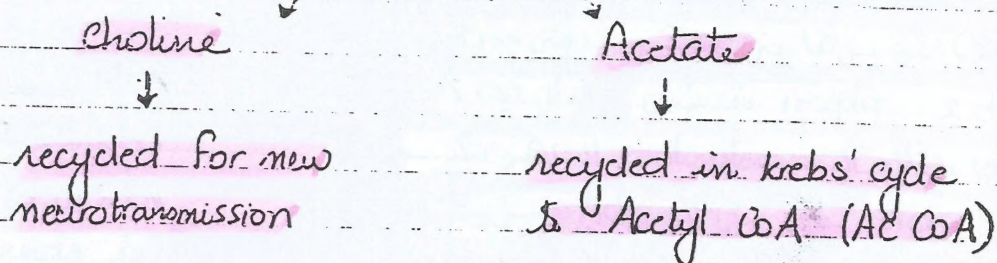


① Synthesis of Ach is catalysed by CAT enzyme (Choline acetyl transferase)

② The process of neurotransmission is voltage dependant.  
حين لما الاشارة بتوصل ال  $Na^+$  يبتدى يخل جوه والى ال  $Na^+$  يفتح  
depolarization وتغير في ال memb. potential فال  $Na^+$  channels يفتح  
وتخل  $Na^+$  والى جنبها بتحق بتغير ال potential ده  
فتفتح برده وتخل  $Na^+$  وهكذا بتستقر ويحجز propagation  
على ال membrane. وبعدين ال  $Ca^{2+}$  يبتدى يخل وده يشجع ال vesicles  
على ان تطلع ال Ach الى جوا

\* Release of Ach from vesicles is done by "Exocytosis".

③ Ach is degraded by cholinesterase enzyme into:



④ Presynaptic receptor:

ده ال هو ال receptor اللى قبل ال synapse  
طب وده ايه ده ؟  
ده بيحسك فيه Ach بره زي زي ال post synaptic receptor  
طب ايه الفرق بين ؟  
الفرق ان لما بيحسك فيه ال Ach بيحل regulation  
ويمنع طرح Ach ال ← بيتحكم في الغليق بين

\* Presynaptic receptor is responsible for regulation (i.e. control)  
ie Acts as a negative (-ve) feed back.



# Cholinergic Agonists

## → "Cholinomimetics".

جمله آوی کلمه دی

2 types

## Direct acting cholinomimetic agents

Indirect acting agents.

دیہاتیں صاحبزادے کے پاس

15.  $\alpha_1$  and  $\alpha_2$  are receptors

دی بتقل ال cholinesterase ال هو بکسر۔

اد Ach ← يقى ال Ach هيزيد

← سبق التأمير زي الاول بس

بهریقه فی مباسرہ

- Indirect acting agents produce their effect by  $\downarrow$  acetylcholine-esterase

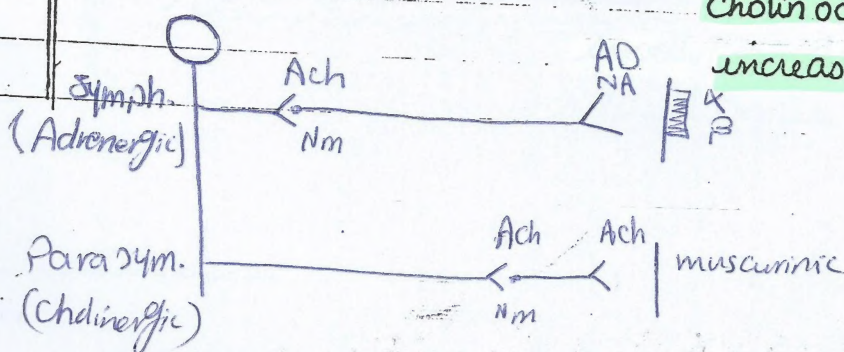
esterase  $\rightarrow$  so ↑ endogenous

Ach core. → and the xss

Ach in turn stimulates

cholinergic receptors to evoke

increased responses





بين خد بالث ، الزيادة دي حفر و في ليا حد ، لاني لو فضلت  
 ازود ال Ach كده من غير تفكير يبق "الى يزيد عن حد قلب  
 ضربه" - ويمكن قلب بسفل في العفلة وقلب بالعكس زي ما حصل  
 في nicotine & conc. nicotine الى شغلهم في الحار ٥٥٥٥  
 وبقى كده antagonists بعد ما كانوا agonists ٥٥٥٥

طبيب نشوف حاجة تانية الى هي :

## CHOLINERGIC RECEPTORS

من اسمها كده ٥٥٥ هي دي ال receptors الى بيشتغل على Ach.  
 وهي نوعين ← M ← Muscarinic (mAChRs)  
 ← N ← Nicotinic (nAChRs)

بين كل واحدة منهم سواء ال M او ال N متقسمة تانية على حسب  
 الامكان الى هي موجودة في ٥٥٥

\* 3 main (mAChRs) occur :

a) M<sub>1</sub> receptors "neural" : → in CNS, gastric parietal cells

• It is selectively blocked by 'Pirenzepine'

b) M<sub>2</sub> receptors "cardiac" : → in heart, also mediate presynaptic inhibition

c) M<sub>3</sub> receptors "glandular" : → in exocrine glands, smooth muscles & causing vascular relaxation (i.e. in muscles lining blood vessels)

Pirenzepine  
Pirenzepine

Pirenzepine



\* All mAChRs are expressed in CNS, activated by Ach & inhibited by atropine

(non selective muscarinic inhibitor)

(non selective muscarinic stimulant)

\* nAChRs (Nicotinic Ach Receptors)

2 types

$N_N$   
(Nicotinic neuronal)  
Central

$N_M$   
(Nicotinic muscular)  
Peripheral

neuronal  
muscular

• Muscular, Neuronal (or peripheral, central) nAChRs differ in their molecular structure & pharmacology.

\*  $N_N$  receptors → in autonomic ganglia, adrenal medulla, CNS.

• Antagonized by: trimethaphan & hexamethonium  
inhibited by

\*  $N_M$  Receptors → In skeletal neuromuscular junction

• Antagonized by: d. tubocurarine, gallamine, atracurium & Suxamethonium (succinyl choline)

persistent depression leads to contraction via initial stimulation leads to  
despolarizing (dli) paralysis leads to relaxation via

neuronal



muscarine  
nicotine  
\* alkaloid

\* ester of choline  
Ach

-9-

طبيب نعالوا نطلم بالتهليل الة شوية عن الة

## Direct Acting Cholinomimetics

احنا قلنا ان دول الة بيشتغلوا على ال receptor على ماول فبيدقوا حاجات شبه ال Ach او بمعنى اصح ممكن يقولوا esters of choline ومن مومن ال esters دي ال Ach . . .

\* The direct acting cholinomimetics can be divided on basis of chemical structure into esters of choline (including Ach) or alkaloids as: muscarine, nicotine.

\* A few of these drugs are highly selective for muscarinic or for nicotinic receptors but many have effect on both receptors as "acetyl choline".

بيشتغل على الة

احنا قلنا ان (nonselective)

\* تشوف كم عنوان كه وكلم نتج ال Direct acting cholinomimetics

1. Chemical structure

2. Pharmacokinetics

3. Pharmacodynamics

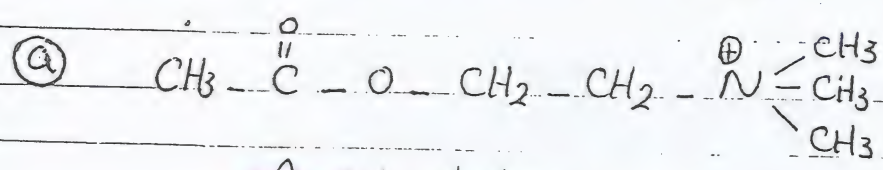
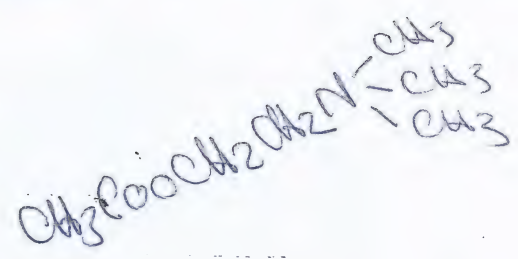
4. Organ effects

عين بيغلوا الة في ال organs (الة الناس بتاخذ الة)

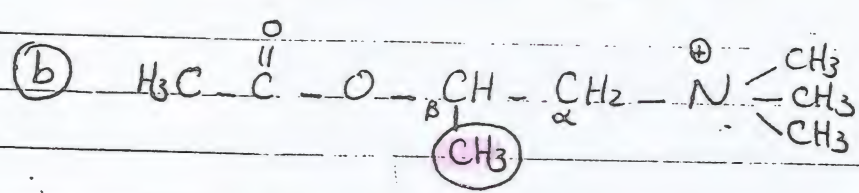
ال تشوف عنوان عنوان كه بالرة . . .



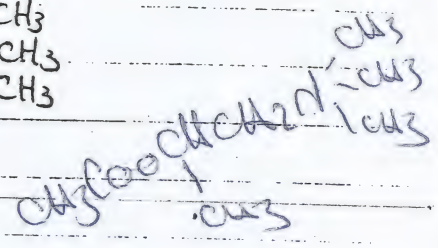
# 1] Chemical Structure :



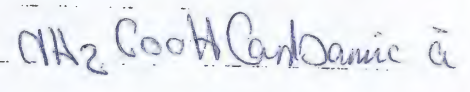
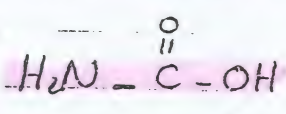
Acetyl choline



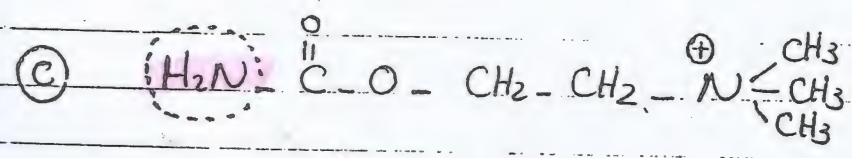
Methacoline  
(acetyl β-methyl choline)



Carbamic acid  $H_2N - \overset{\overset{O}{\parallel}}{C} - OH$



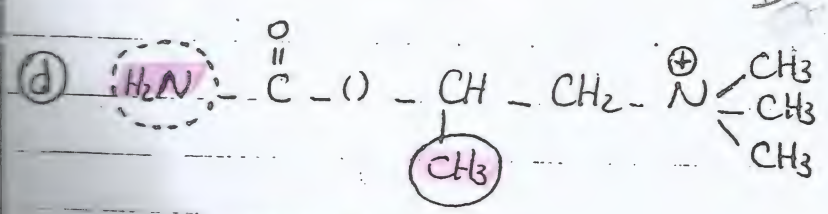
methacoline و Ach مرة على الـ



Adh لما دخل على الـ  
شلت بس الـ  
(NH<sub>2</sub> حبيبة)

Carbachol  
(Carbamoyl choline)

Bethanechol



لما دخل على الـ  
methacholine

Bethanechol  
(carbamoyl β-methyl choline)



## 2] Pharmacokinetics :

\* Choline esters are poorly absorbed & distributed in the CNS.

\* Although all are hydrolyzed in the GIT → they differ markedly in their susceptibility to hydrolysis by cholinesterase in the body.

وهذا إلى بيكسر كل ال esters دي بس حسب البنية  
يتبع كل واحد فيهم ببنية مختلفة تأثير العنصر ده على  
بعض مثلاً :

a) Ach : is very rapidly hydrolyzed

بيتكسر بسرعة أوى

∴ large amounts must be given intravenously to achieve conc. high enough to produce detectable effects (non specific) that terminate within seconds.

بعض علشان استخدم ال Ach كله بينا تأثير جامد لازم ادينا  
بكمية كبيرة لأنه من بيستخدم وبيتكسر بسرعة جداً

b) Methacholine :

الفرق بينا وبين ال Ach ← methyl gp فى ال β position  
ورده بتخليه

More resistant to hydrolysis

Carbamic esters الى صم :

طرح وال



c) Carbachol & bethanechol:

are still more resistant to hydrolysis by cholinesterase & therefore have longer duration of action.

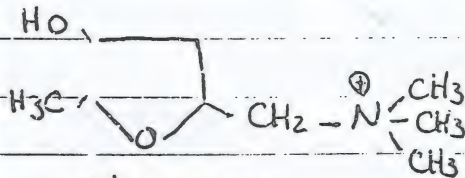
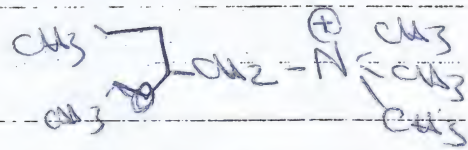
لا يزالان مقاومين للهضم في العضلات

CVB:

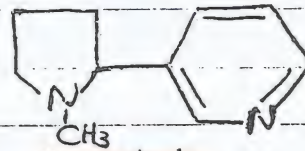
The  $\beta$ -methyl gp (in Methacholine, bethanechol)  $\rightarrow$  reduces the potency of these drugs at nicotinic receptors (i.e. more selective for muscarinic receptors)

هذا المركب هو استر الكولين الطبيعي (carbamate) وهو مقاوم للهضم في العضلات

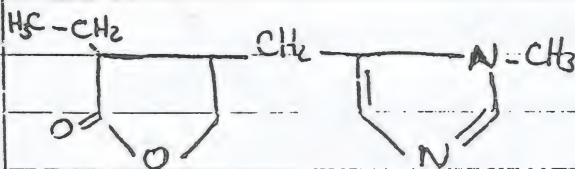
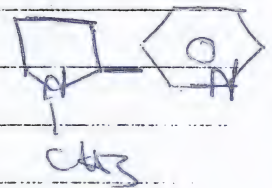
\* Chemical structures:



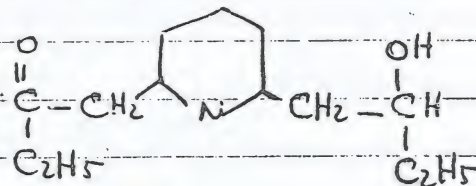
Muscarine



Nicotine



Pilocarpine



lobeline



لو ركزنا في ال structures هتلاقي ان كل ال choline esters poorly absorbed in CNS وانه ال quaternary amm. cpds

لكن هتلاقي ان ال alkaloids  $\rightarrow$  3ry  $\rightarrow$  muscarine ال هتلاقي 3ry بس هتلاقي 4ry وعلشان كده هتلاقي واحد فيهم بيجعل absorption

طرح تعالوا نشوف ال Pharmacokinetics ال alkaloids

\* The 3ry natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) are well absorbed from most sites of administration

a) Nicotine :  $\rightarrow$  a liquid, sufficiently lipid soluble to be absorbed across the skin.

b) Muscarine : 4ry amine  
- less completely absorbed but is toxic when ingested & even enters the brain.

c) Lobeline : is a plant derivative similar to nicotine.

\* These amines are excreted chiefly by the kidneys.

- Acidification of urine  $\rightarrow$  accelerates the clearance of 3ry amines.

زي ما اخذنا لو تاكرين في الما بزره التانيه لما قلنا ان ال weak bases

acidification ال low pH ال entrapment

reabsorption و ال urine ال excretion و clearance



### [3] Pharmacodynamics :

يعني الادوية دي بتشتغل ازاى على الجسم

#### \* Mechanism of action:

phospho-  
lipase / cAMP

a) Muscarinic receptors: G-protein Coupled R  
activation of muscarinic receptors  
implicates DAG in the opening of smooth muscle  
Calcium channels  $\rightarrow$  IP3 releases Calcium from  
endoplasmic & sarcoplasmic reticulum (for  $H_3$ )

Activation of receptors also  $\uparrow$   $K^+$  flux across cardiac  
cell membranes ( $H_2$ )

This effect is mediated by the binding of an activated  
G protein directly to the channel

الكثير ده مش عارف حلو و في المخابر و الامتحانات  
ارجوا افروه من ههنا

b) Nicotinic receptors: Ion-channel Coupled R  
When occupied by an agonist  $\rightarrow$   
causes a conformational change in the protein  
(i.e. channel opening)  $\rightarrow$  allows  $Na^+$  &  $K^+$  ions to  
diffuse down their conc gradient rapidly.



\* Binding of an agonist to the receptor  $\rightarrow$   $\uparrow$  the probability of channel opening & depolarization of the nerve cell or neuromuscular end plate membrane.

طب لو زاد ال agonist ده هيجعل ايه ؟

Prolonged agonist occupying of the nicotinic receptor abolishes (يقال اوى او يوقف) the effector response, i.e. the post ganglionic neuron stops firing & the skeletal muscles relax.

i.e. it prevents electrical recovery of the post junctional membrane, thus a state of "depolarizing blockade" is induced.

ايه الكلام الكبير ده ؟

انا الطيب انى يحمى ال agonist هيجعل فى ال receptor ويمنع ال effect اللى هو مثلاً contraction بتاع عضلة ، جمل ده طب انا لو زودت جرعة الدواء ده ، هل انتا بيزيد ؟! لا بسف لا ، هنا "الى يزيد عن حده يقلب ضربه" فلا كسرة الدواء بيزيد اوى هيووقف العلية ويجعل relaxation of muscle و كده يبقى ال receptor حمله blocking نبي اللى عمله ال conc. nicotine

احنا كده اخدنا ٣ عناوين تحت ال Direct acting cholinomimetics

فماضينا آخر عنوان وهو ال :

٤- organ effects

وهنشوف فى تادىرها على :

- eye.

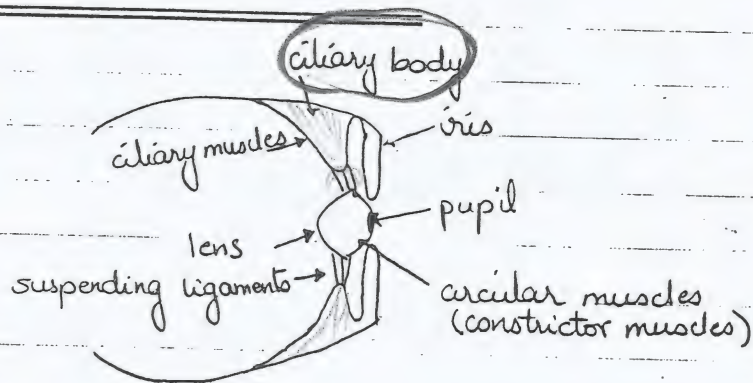
- CNS

- Neuromuscular junction



مطلوب ← قبل ما نبدأ ، في حصة الدكتور شرحها على أن  
 accommodation for near or far vision  
 سيقول الفهم يتبع العين و (أي) يتقل

## ① Parasympathetic stimulation :

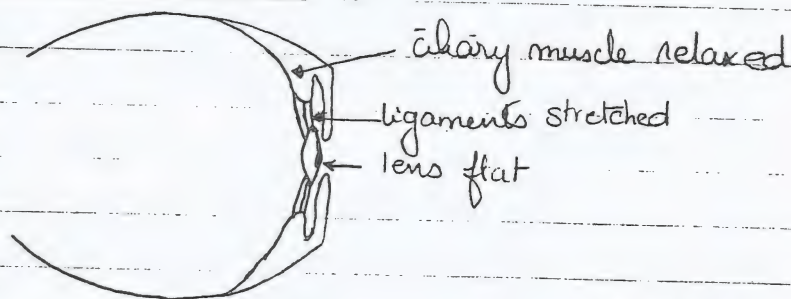


↓ contraction      إلى حد ما ciliary muscles      إلى حد ما

∞ ligaments will be relaxed

∞ lens is more convex → accommodation for near vision

## ② Sympathetic stimulation :



parasymp إلى حد ما  
 ciliary muscle relaxed → ligaments stretched → lens is flat or less convex → accommodation for far vision



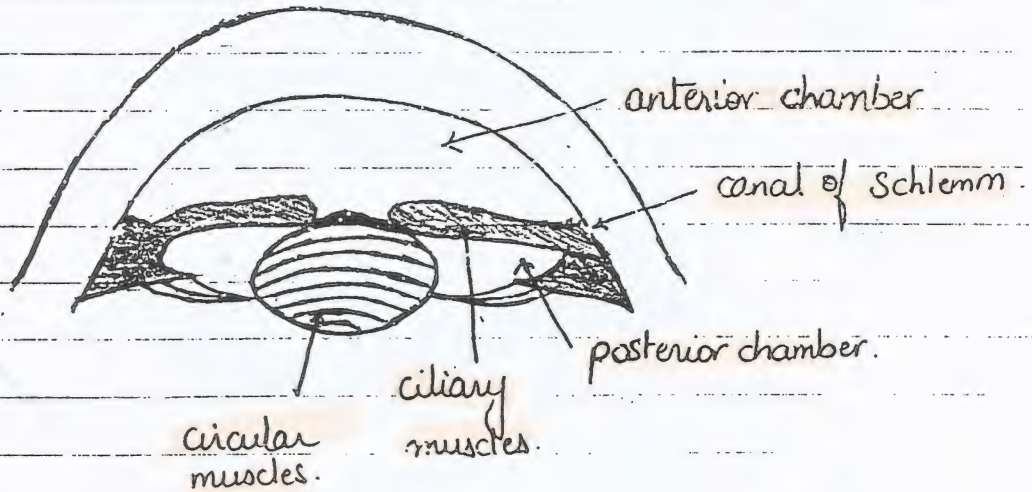
## 14 Organ Effects :

- \* Most of the direct organ system effects of muscarinic cholinergic stimulants are readily predicted from a knowledge of the effects of parasympathetic nerve stimulation and the distribution of muscarinic receptors.
- \* The effects of nicotinic agonists are similarly predictable from a knowledge of the physiology of the autonomic ganglia & skeletal muscle motor end plate.

منظم الكلاز و الدم الى جانب

### A) Eye :

الاول كمنشوف رسمه كده للعين على نفع الكلاز  
الى هيقال عليه بعد كده



هشع العين الاول على نفع ونجد كده نكتب المسدود  
المuscarinic R فعال contraction للموسين من العيالات الموجوده

circular m.

ciliary m.

لو فكر منه المفاضلة السابقة

Parasymp.  
innervatn,

كانت منه الحاجات التي لها  
Dual innervatn. ليس



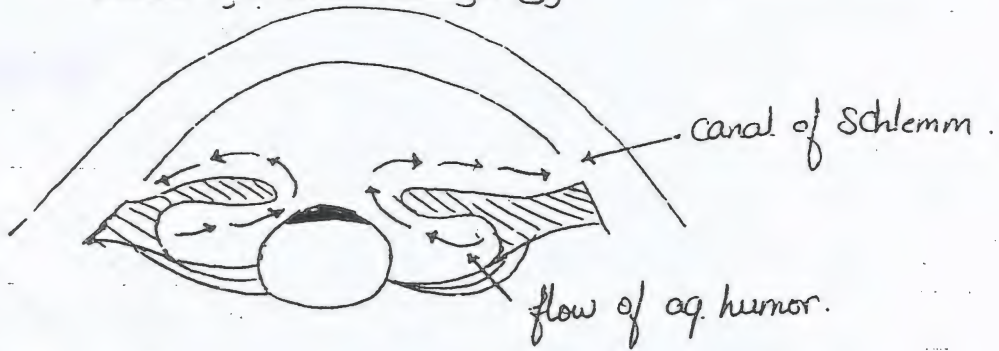


الـ circular m. كمتقل myosis يعني انقباض كمتنقبض اما الـ  
accommodation for near vision ← contraction لما يحصل contraction  
ciliary m.

علما يحرق يشوف كولين ... بين في نفس الوقت لما يحصل  
contraction هتبعد عن الـ ... طب وايه الفكرة في كده ؟  
اقولكم انا الفكرة ...

في حاجة اسمها aqueous humor ده بيتعمل في الـ posterior chamber  
وبيرجع للـ anterior chamber ويتخزن هناك ... ده مسئول انه  
يفتح ضغط العين ... حلوه ؟  
طيب ، بس هنتقش يزيد ادي علينا كده ضغط العين بيزيد  
وده مسئول كولين ، فلانم اتخلص منه ، بين ازاي ؟

لما الـ ciliary m. بيحصل contraction بيتفتح فيسمح بمرور  
الـ aq. humor من الـ posterior ch. ، طب وبعدين هيرجع في الـ  
مخروط في قناة بيرجع فيها اسمها canal of schlemm. بين القناة  
ده قافل علي الـ ciliary m. لكن لما بيحصل contraction بيتجدع  
وبالتالي هيجعل drainage للـ aq. humor ده ...  
زي الرسمة اللي جاية دي ...



يارب اكون عرفت اوصل المعلومة ...  
وعلى الجموع انا تحت امركم لولسة مش  
واضحة ...

تعالوا نكتب الكسيتين دول بطريقة (تظف) شوية ...



\* Muscarinic agonists instilled into the conjunctival sac causes contraction of:

1. the smooth muscle of the iris sphincter <sup>Circular muscle</sup> → resulting in miosis (circular muscles of constrictor pupile)

2. the ciliary muscle → resulting in accommodation for near vision

\* As a result → (a) the iris is pulled away from the angle of the anterior chamber & (b) the trabecular meshwork at the base of the ciliary m. is opened.

canal of Schlemm

Both effects facilitate aqueous humor outflow into the canal of Schlemm, which drains the anterior chamber.

## (B) CNS:

\* The CNS contains both: muscarinic & nicotinic receptors.

\* The CNS effects of synthetic muscarinic agonist

"Oxotremorine" are: tremor, hypothermia and antinociception

- These effects were lacking in mice with homozygously mutated  $M_2$  receptors

## Oxotremorine

Tremor

hypothermia  
& temp?

antinociception

Oxotremorine

antinociception



- \* The mild alerting action (مُنبِّه) of nicotine absorbed from inhaled tobacco smoke is the best known of CNS effects.

In larger conc., nicotine induces → tremors, emesis (vomiting) and stimulation of the respiratory centre

At still higher levels → nicotine causes convulsions (تشنجات) which may terminate in fatal coma.

insecticide والتأثير بنجاح nicotine هو غير انتقائي non selective فيقتل الحشرات ويهيج الإنسان كمان.

- \* DiMethylPhenyl Piperazine (DMPP) → (a synthetic

nicotinic stimulant used in research) is relatively free of these central effects as it doesn't cross the bbb

وعلامة أنه حتى يوصل للدخول وحتى يبين الـ CNS effects ترى الفرق

bbb: Blood brain barrier.

وأخر حاجة هتسوف التأثير عليها

### (C) Neuromuscular Function :

- \* The nicotinic receptors on the neuromuscular end plate respond to : acetylcholine & nicotine.



\* When a nicotinic agonist is applied directly → an immediate depolarization of the end plate results, caused by increased permeability to  $\text{Na}^+$  &  $\text{K}^+$  ions. → causing contraction of the muscle.

\* Depolarizing nicotinic agonists that are not rapidly hydrolyzed (like nicotine itself)

يعني من بيتكسر بسرعة فبيغفل شغل ال receptor

↓  
cause rapid development of depolarization blockade.

\* طبيب احنا في ده كنا بنتكلم عن ال Direct acting cholinomimetics  
وجكينا عنهم بالتفصيل الممل ..  
تعالوا دلوقتا نشوف بقى ازاى

## Indirect Acting Cholinomimetics

فنتكلم فيهم زي التالى عن :

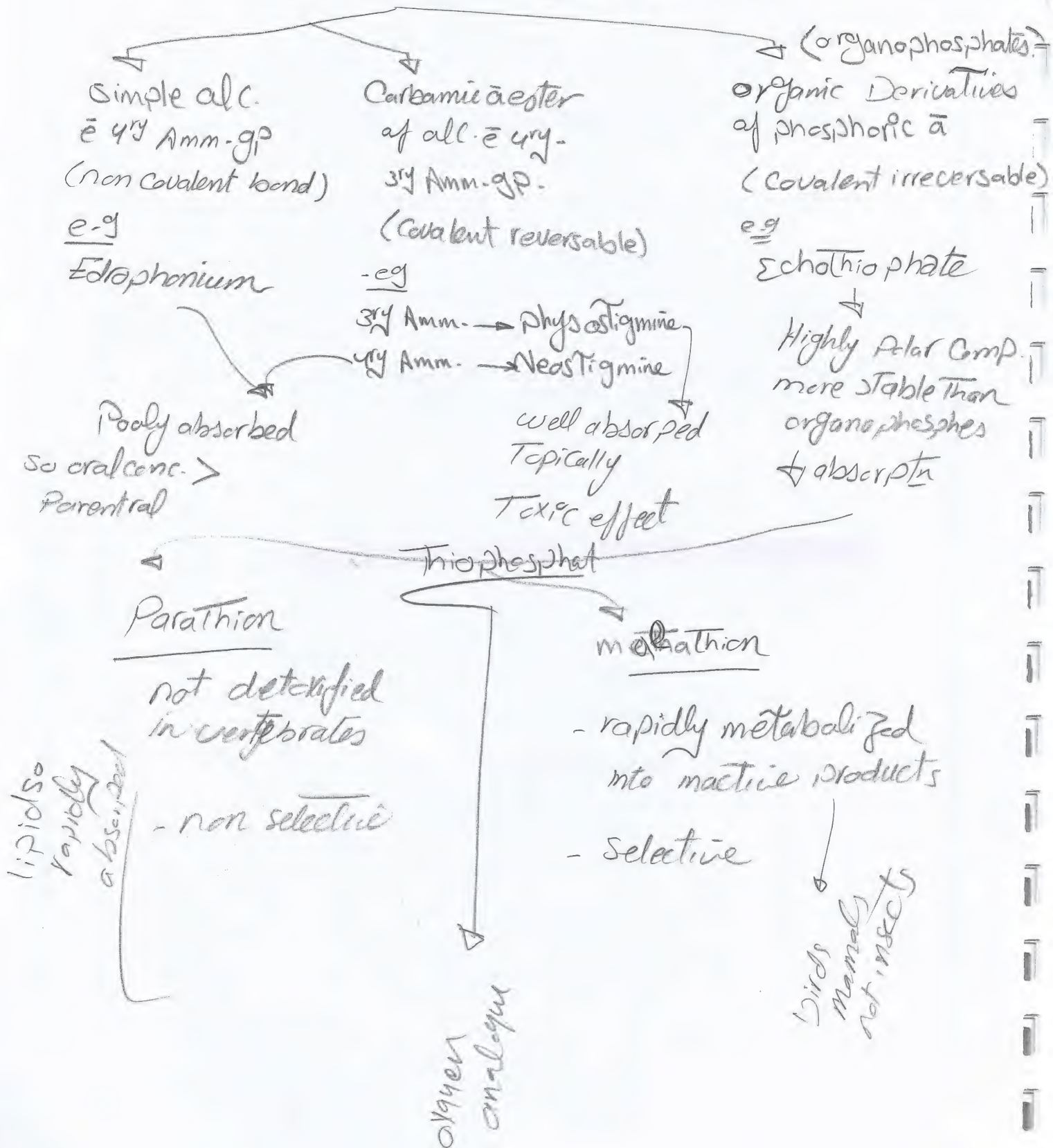
1. Chemistry
2. Pharmacokinetics
3. Pharmacodynamics (MOA)
4. Effects → CNS  
→ CVS

يلا نشوف واحد واحد منهم .....



\* Direct Acting Cholinomimetic \*

[ $\uparrow$  Cholinesterase]  $\rightarrow$   $\uparrow$  ACh





## 1] CHEMISTRY:

↓ cholinesterase enz. يستعمل عن طريق  
التي يكثر الـ ACh و تستوف الكثرة التفصيل أكثر في الـ MOA

\* The commonly used cholinesterase inhibitors fall into 3 chemical groups:

- (1) Simple alcohols bearing a 4ry ammonium gp (non covalent binding) eg: "Edrophonium"
- (2) Carbamic a. esters of alcohols bearing 4ry or 3ry amm. gps (carbamates, eg: "Neostigmine" or (3ry) "Physostigmine") → (covalent reversible) (4ry)
- (3) Organic derivatives of phosphoric a (organophosphates, eg: "Echothiophate") → (covalent irreversible)

## 2] PHARMACOKINETICS:

\* Absorption of (4ry carbamates) (neostigmine, pyridostigmine) is predictably poor, so much larger doses are required for oral administration than for parenteral injection.

وهو طبيعي لأن الـ oral route صياغة وقت الأول علامة يوجد للم  
وهو أصلاً الـ absorption بآلية قليل فالة) هيفضل هيفضل قليل الـ  
فلازم الـ جرعة أكبر من لو injection



- (3ry)  
\* **Phsyostigmine**, in contrast, is well absorbed from all sites & can be used topically in the eye.  
It is distributed into the CVS & is more toxic than the more polar 4ry carbamates.

لا ى ال abs. بتاى صحت كى ال 3ry ال absorption بتاى  
اعلى بكثر فتاىها بىقى اجد وكن بىقى toxic.

- \* The carbamates are relatively stable in aqueous soln.  
طرب لىكس روا ازاى جد ما يعلوا صوفهم IS!

they can be metabolized by non specific esterases in the body as well as by cholinesterase

However, the duration of their effect is determined chiefly by the stability of the inhibitor-enzyme complex, not by metabolism or excretion

بىقى لىما انوار ده لىكس روا ال enzyme صوفهم حاسب ال ال  
او ال stability بتاى حاسب ازاى < وكن ى ال ال صوفهم ال  
duration of action بتاى

- \* The **organophosphate** cholinesterase inhibitors (except for **Echothiophate**) are well absorbed from the skin, lung, gut & conjunctiva as well as the CVS (may cause CVS toxicity)  
so they are dangerous to humans & highly effective as insecticide.

صوفهم الاشى

طرب ال الفكرة روا ال Echothiophate IS OS



\* Echothiophate is highly polar & more stable than most other organophosphates. (absorption)

∴ It can be made in aqueous soln for ophthalmic use & retains its activity for weeks.

absorption سريعة

\* The thiophosphate insecticides (Parathion, Malathion) → are quite lipid soluble & are rapidly absorbed by all routes.

• پس هر بیستندوا که علی طریقی اول ما بیخودا الحسم ؟

الاجابة : لا ، طب لی ؟

∴ They must be activated in the body by conversion to the oxygen analogue.

• طب پس احنا عارفین ان ال Malathion ده بیهیستخیم کمید حشری و نخال ، طب لای که وه و ممکن یضیر الانسان کمان ؟  
- الفكرة ان الانسان عنده mechanism ثانية بتکسر ال malathion ده و تخلیه inactive ، ال mech. ده مش موجوده فی ال insects .

\* Malathion is also rapidly metabolized by other pathways to inactive products in birds & mammals but not in insects → ∴ it is considered safe enough for sale to the general public (i.e. selective)

But Parathion is not detoxified effectively in vertebrates (i.e. not safe)

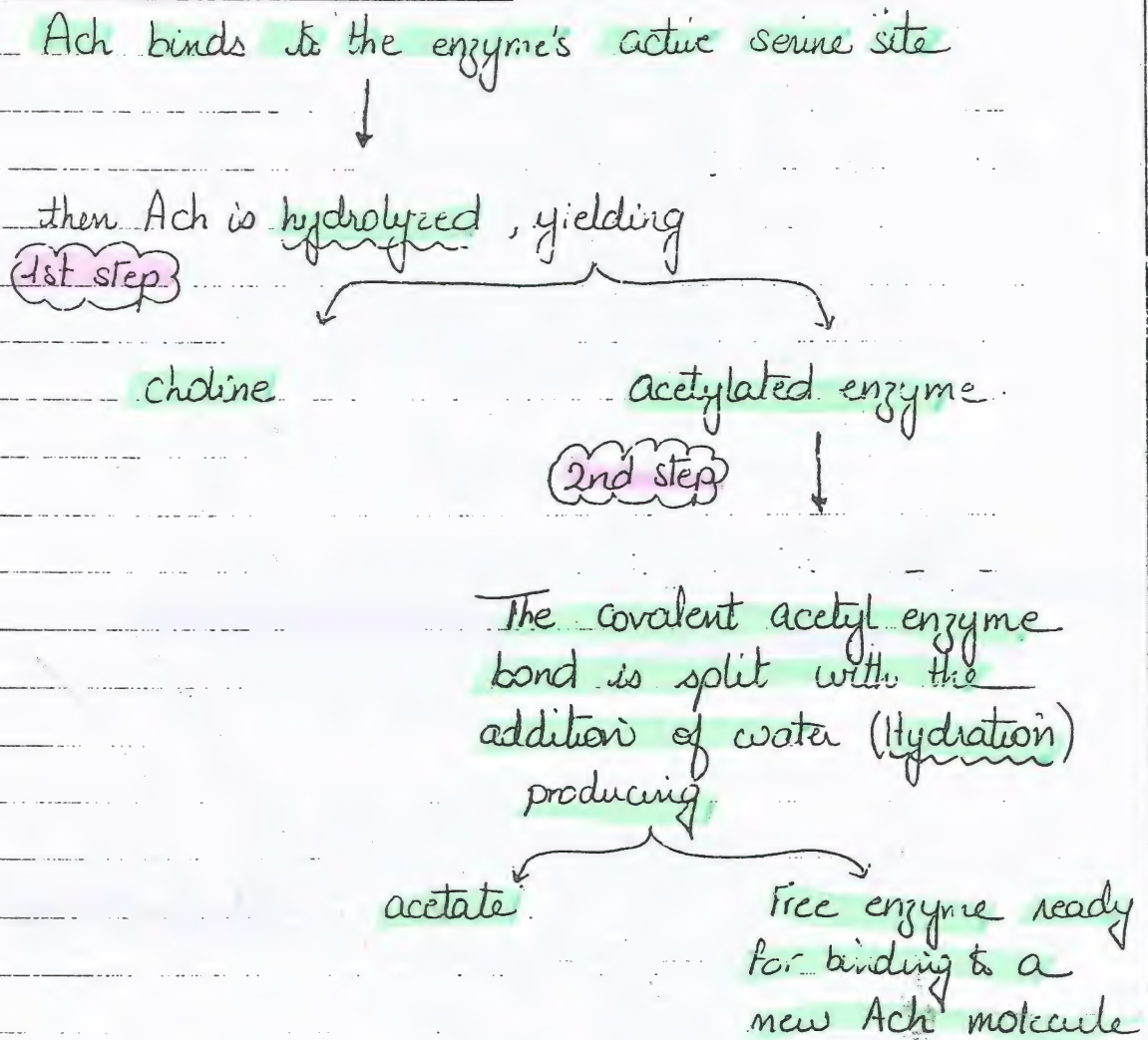


### 3 MOA : (Mode of Action)

- \* Generally : Cholinesterase inhibitors ↑ the conc. of endogenous Ach at cholinergic receptors by inhibiting acetylcholinesterase.

دی فکر عامه که عن الی بیچم : تعالوا نشون اهد  
ال enzyme ده بکیر ال Ach ازای و بچین نشون ازای  
الادویه دی بتقلل ال enzyme.

#### \* MOA of cholinesterase on Ach :





طبيب الادوية بقى لما بتحسك فى ال. enj. ده بتحل ايه ؟

\* MOA of cholinesterase inhibitors on cholinesterase enj.

لما ال carbamates هتسك الى هتسك :

(1) The Carbonylated enzyme is considerably more resistant to the end (Hydration) process → and this step is correspondingly prolonged to 6 hrs.

(2) The covalent phosphorylated bond (as in organophosphates) is extremely stable and hydrolyzes in water at a very slow rate

\* The phosphorylated enzyme complex may further undergo a process called "aging"

• ايه دى ؟

احنا قلنا ان phosphorylated-enz. complex بيتى - stable اوى  
وبيقت قتره طويله ، فتمكن نيجد aging الى هتسك  
فى bond من ال bonds الى بيتى ال oxygen ، phosphorous  
وبالتالى ده تبيقت اكر ال complex الى بيتى phosphorylated enj.  
وتمتليها شى تنكس خالى حتى بعد مدة طويله

→ ralidoxime

• طرب هو انا اصله ممكن انزى انك ال complex ده ؟

Pralidoxime بيتسك ب strong Nucleophils زى نواه اسما  
ويرجع ال cholinesterase . بس ده مش هيجل زى لو اسما  
قبل ما يجل ال aging

\* The process of Aging involves the breaking of one of the oxygen-phosphorous bonds and further strengthens the phosphorous-enzyme bond.

Pralidoxime





- If given before aging has occurred, strong nucleophiles like "Pralidoxime" are able to split the phosphorous-enzyme bond & can be used as "Cholinesterase regenerators" for poisoning.

#### 4. EFFECTS :

- \* The most prominent pharmacological effects of cholinesterase inhibitors are on: the Cardiovascular system, GI system, the eye & the skeletal muscle neuromuscular junction.
- \* Since the key action is to amplify the actions of the endogenous Ach, the effects are similar to the effects of the direct-acting cholinergic agonists.

بين الاشارة الى ان زيادة contraction او احوال muscle واحد هي شغل مباشرة على muscle والتاثير يزيد ال Ach ويزيد من contraction

\* هتسوق التأثير بتاثيره على حاجتين :

1. CNS
2. CVS



## ① CNS :

In higher conc., the lipid soluble cholinesterase inhibitors cause generalized convulsions, which may be followed by coma & respiratory arrest.

## ② CVS : ( CardioVascular System)

Negative chronotropic, dromotropic & inotropic effects are produced

↓ rate of contraction

↓ conduction velocity across nerve fiber

↓ force of cardiac contraction

\* لا يثقل في rest من مضاعفات القلب ويقلل حاداً

Indirect Acting cholinomimetics

تعالوا نسوف دلوقتى ع مومنتوات صغرة والسوايح دى عامة بكون ل direct وال indirect :

1. Clinical uses of cholinomimetics :
  - a) Eye
  - b) GI & urinary tract
  - c) Neuromuscular junct<sup>n</sup>
  - d) CVS

### 2. Toxicity

### 3. Toxic manifestations

### 4. Management

معلش ٥٥٥ انا عارفة انى كنه لوقت عليكم اوى ٥٥ بس خالص  
صانت ٥٥٥ الحرة الى فاضل مش كبير ٥٥٥٥



## \* Clinical uses of cholinomimetic :-

[1] Glaucoma  $\begin{cases} \rightarrow \text{open angle glaucoma (chronic - simple)} \\ \rightarrow \text{closed " " (Acute - narrow)} \end{cases}$

[2] GIT & U-TI  $\begin{matrix} \downarrow & \downarrow \\ \text{regulate} & \text{urinary} \\ \text{motility} & \text{Retention} \\ \text{Post operative} & \text{Post operative} \\ & \text{Apost Partum} \end{matrix}$  e.g. Bethanechol.  
Neostigmine  
Pilocarpine

[3] C.N.S.  $\downarrow$  of Alzheimer

e.g. Tacrine - donepezil - Rivastigmine

metformate  
 $\downarrow$   
schistosomiasis

on dialy ??

half long life time and lack of hepatotoxic effect of Tacrine

[3] Neuromuscular junction disease (myasthenia gravis)

e.g. • Edrophonium  
• Neostigmine



## 41 Clinical Uses of Cholinomimetics

### A EYE :

الأول هنك شوية كنه عن مرض ال Glaucoma اللى هو السق الزرق

\* Glaucoma : a disease of the eye characterized by increased IOP (Intraocular pressure), atrophy of optic nerve → and produces defects in vision field.

(Glaukos = bluish green)

\* مرض المرء به قدامه بوقية :

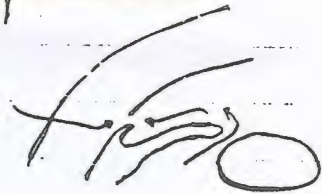
#### 1- Open angle glaucoma :

try glaucoma in which aqueous humor has free access to the trabecular mesh work.

• Synonyms : Chronic or Simple glaucoma.

ده النوع الطبيعى بس هنا العلية  
بتحصل ببحوية شوية بس بتفتح عاين  
وال aq. humor بيطلع بس عقبال ماله  
بيحصل بيكون الضغط زائد. وبما ان القناة  
مفتوحة بنسبها open angle glaucoma

open  
angled

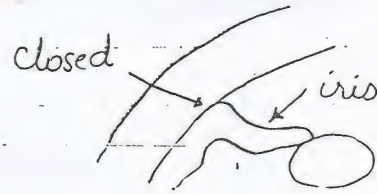




## 2. Angle Closure Glaucoma:

is a type of glaucoma in which contact of iris with the peripheral cornea excludes aqueous humor from the trabecular drainage mesh work.

- Synonyms: Acute glaucoma, closed angle glaucoma, narrow angle glaucoma.



هذا ال iris قاذلة على ال cornea بطريقة مغلقة على ال canal ويتم إغلاق منقذ humor ال change of ال IOP ال عتال يزيد حاد ويمكن يسبب العمى . . . .

فهو يتوايه من المية الزرقاء في ال -  
كل الكاوي في عتاله فهم الكاويين ال جايين دول . . . .

ازاي بنستخدم ال cholinomimetics علشان اعالج ال Glaucoma

- \* In the past, glaucoma ( $\uparrow$  IOP) was treated with either direct agonists (pilocarpine, methacholine, carbachol) or cholinesterase inhibitors (physostigmine, demecarium, edrophonium, isofluorophate (Diisofluorophate) IOP as ointment).



\* For chronic glaucoma, these drugs have been replaced largely by topical  $\beta$ -Blockers & Prostaglandin derivatives.

\* يعني ايه ؟!

لحنا عارفين ان سبب ال glaucoma هو ضغط عالى فى العين وسبب الضغط ده اى بيطلع عندي aq. humor ومن جرفا اقله منه ، طب ما انا ممكن اخل السونج دى باقى اقله املاى طلع ال aq. humor وهو ده الى بيحله ال  $\beta$ -Blockers بتقل طلع ال aq. humor ← treatment ده

### 3} Gastrointestinal & Urinary Tracts:

i.e. using of cholinomimetics in → GIT & U-T-I???

(1) In clinical disorders that involve depression of smooth muscle activity without obstruction

(2) Postoperative ileus (atony or paralysis of stomach or bowel following surgical manipulations)

بعد العمليات الجراحية بيتر فيه قنطرة فى حركة ال GIT فلما ادى الانوية دى تنضبط الدنيا وتنقل activation ال GIT

(3) Urinary Retention (Postoperative or Postpartum)

بعد العمليات : بعد الولادة :

\* The most widely used agents are:

bethanechol, neostigmine

Bethanechol  
Neostigmine



\* Pilocarpine has long been used to ↑ salivary secretion.

### ⊕ Neuromuscular Junction

\* "Myasthenia gravis" → a disease affecting skeletal muscle neuromuscular junctions.

Frequent findings are: ptosis (ارتخاء في جفن العين) و difficulty in swallowing & speaking, extremity weakness & ultimately respiration (Sensitivity to aminoglycoside antibiotic) (irregular).

من وافيح ان مرون بعد relaxation فاعادة

ex

ادله حالة تزود ال contraction

1. Edrophonium: used as a diagnostic test for the disease and the long term therapy.

2. Neostigmine, pyridostigmine or amibenonium (every 4-6 hrs)

\* Antidote for neuromuscular blockade following surgical anaesthesia → Neostigmine & Edrophonium (IV, IM).

\* Antimuscarinic drug intoxication (by atropine, TCA)

tricyclic antidepressants

↓ blocking M<sub>2</sub> receptors  
Phyostigmine → ↑ ACh → removes competitive blocker  
receptor

this Phyostigmine can reach the CNS.



## [ Toxicity ]

- 1) - ↑ Dose of relaxants → Paralysis
- 2) - ↑ Dose of contractants → Convulsions
- 3) - Toxic effect of pesticides  
(100 organo, phosphates - 20 carbamates)

4) - war nerve gases

Cholinesterase inhibitor gases have lethal effect



## D CNS :

\* Tacrine, donepezil & Rivastigmine are acetylcholine-esterase inhibitors that appear to have modest clinical benefit in treatment of cognitive dysfunction in Alzheimer's patients.

\* Donepezil → may be given once daily, why?!

- because of its long half life & it lacks the hepatotoxic effect of Tacrine.

\* Metr. Fonate was used for the treatment of Schistosomiasis.

\* کہ ایک اور دوا ۵۰۰ میجر اوی صبح ۱۵  
تھووا شے تک دوپہر ۱۰ ورنہ ۱۵ صبح ۰۰۰۰

## 2 Toxicity

\* The acute toxic effects of the cholinesterase inhibitors, like those of the direct acting agents, are direct extensions of their pharmacologic actions

یعنی اسکی اثرات ہیں relaxation ہے لا یزید ہے  
والی ہے contraction ← لا یزید ہے  
paralysis ہے  
convulsions ہے



## \*Toxic Manifestations\*

### Muscarinic

#### DUMBELS

Diarrhea  
urination  
miosis  
Bradycardia  
Emesis  
lacrimation  
sweat  
salivation

### Nicotinic

#### MATCH

muscle Twitching  
Adrenal hyperActivity  
Tachycardia  
Cramping  
Hypertension

### C.N.S

- Confusion
- loss of coordination
- " " reflexes
- convulsions
- Paralysis in c  
Respiratory



\* The major source of such intoxications is pesticide use

لها بياض الانسان او بياضها بياض toxicity. 100 organophosphates & 20 carbamates ← كثير

\* The "war nerve gases" (Tabun, Sarin & Soman) are among the most potent synthetic toxins known (they are cholinesterase inhibitors) → they are lethal to laboratory animals in microgram doses.

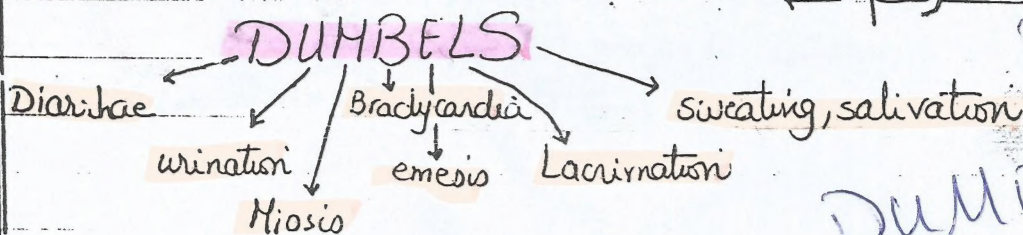
### [3] Toxic Manifestations

يعني اي ال symptoms بآت ال toxicity ال  
هشوة اي على الانسان ده ؟

هشوة لو ال toxicity حبلت بسبب حاجات بتشتغل على ال Muscarinic R<sub>s</sub> او ال Nicotinic R<sub>s</sub> او استعملت على ال CNS ال فاهلها الاستجابة ...

#### (A) Muscarinic :

→ miosis, salivation, sweating, bronchoconstriction, vomiting (emesis), diarrhoea, bradycardia, hypotension, urination & lacrimation  
جميع اعضاء في كلمة كده قالها الدكتور على انه حرف



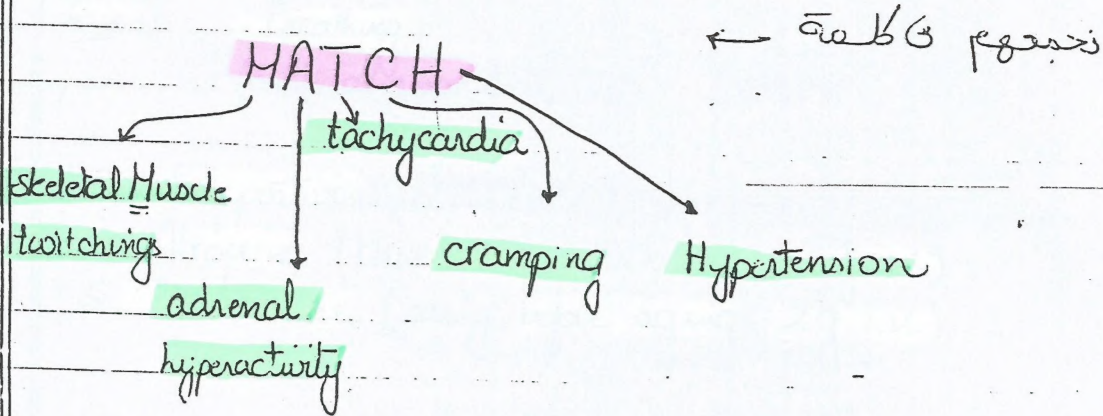
**DUMBELS**

**DUMBELS**



### (B) Nicotinic :

(حركات لا إرادية في العضلات)  
(contractions) → skeletal muscle<sup>t</sup> twitchings & cramping ,  
fasciculations & eventually severe weakness  
and paralysis (respiratory) due to sustained  
depolarization.  
also adrenal hyperactivity, tachycardia & hypertension



### (C) CNS :

→ confusion, ataxia (loss of coordination), loss of  
reflexes, convulsions, coma & central respiratory  
paralysis

→ Actions on the Cardiovascular centers in the  
medulla oblongata lead to hypotension.

ودمع آخر عنقوان في المعاصرة العظيمة دي  
مجلس الاعرافة اني طوكت عليكم  
بس انا مجتهد في حاجة من عندى

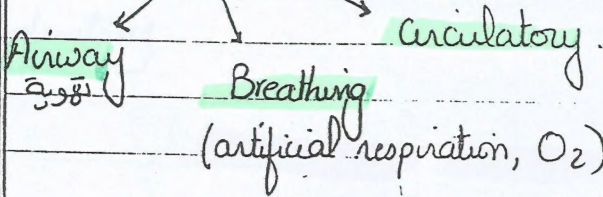


## 4 Management

هناك ازالة ال toxicity الى حد ما!

1. Decontamination اسهل مع التسدد

2. A, B, C



3. Supportive (convulsions, shock)

4. Atropine (Muscarinic blocker, 4 mg i.v.)

5. Pralidoxime (early, before aging, 2g i.v.)

\* الحمد لله المحاضرة كانه خلقت  
 \* يارب تكون للعامة ومهلت وتكونوا مستوعبين  
 المحاضرة والمادة دي حلو ادي ٥٥٥  
 لو نزل اي حاجة عيش واضحه او مش فاهمها ٥٥٥  
 مش هنتقواكم بعين ٥٥ نقالوا اسألوا على طول ٥٥٥  
 وأخيراً ٥٥٥٥٥

احنا بجد فحتاجين صلوا تكم  
 اوى اوى اوى

٥٥٥٥٥٥٥٥٥٥

اوعدوا بتسونا

كن مطمئناً جداً ٥٥٥  
 ولا تفكر في الامر كثيراً ٥٥٥  
 بل دع الامر لمن بيده الامر ٥٥٥